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INCLUSION COMPOUNDS

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(Conclusion)

B. With Cagelike Spaces.—These inclusion compounds are the true clathrates (9), which are formed by locking up one molecule of a guest compound in the cagelike hollow space formed by the combination of several molecules of the host compound. Here, again, as in the previous type, a given host can accommodate a variety of guest compounds. The main characteristics of these inclusion compounds are the following:

(a). Since it is through the ability to form a cagelike structure that certain compounds can act as hosts, slight variations in structure can render a molecule unsuitable. Hydroquinone and resorcinol are a case in point. Although the latter has the same functional groups and general properties as the former, it cannot crystallize in such a manner as to form a cage in its center.

(b). The structure containing the cage should be strong enough to allow the guest to be freed only upon destruction of the cage. This is done by heating or dissolving the clathrate, whereby the bonding energy is exceeded and the complex is destroyed.

(c). Geometrical, rather than chemical, characteristics determine whether or not a pair of compounds can form a clathrate. Once it has been found that a prospective compound can act as host, it must be determined whether the guest will fit into the available space, since it can only enter the cage before the whole structure is formed. If it were too large, it would prevent the "trap" from closing; if too small, it would be able to slip out. Hydroquinone, for instance, can enclose methanol and argon but not ethanol (too large) or helium (too small).

(d). There is a limiting composition for any given clathrate, and this will be determined by the number of cages available. These can become filled or not, according to the circumstances which surround the formation of the clathrate. Therefore, if the host is dissolved in the guest, it is likely that most of the cages will become occupied, but, if an indifferent solvent is used, the structure might be completed before all possible guest molecules are in place. It must be remembered that it is just as difficult for a guest to enter a cage already formed as it is for it to leave.

Several well-known compounds inexplicably gave substances difficult to identify

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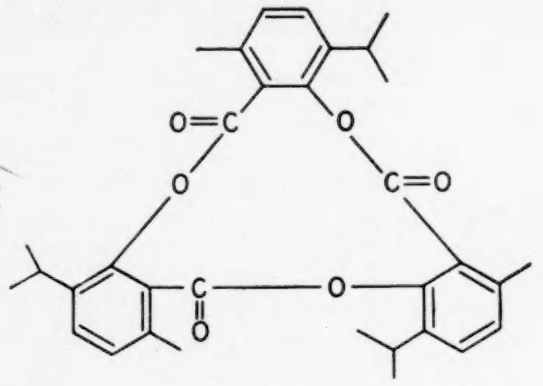
when recrystallized under certain conditions; these were found to be clathrates. An example is β-quinol, which is nothing more than hydroquinone with included methanol.

1. Hydroquinone.—A good part of the work done on clathrates was performed with this compound, and, as guests: methanol, acetonitrile, H_2S, SO_2, HCl, HBr, HCN, CO_2, C_2H_2, A, Kr, and Xe. The ideal formula is three hydroquinones per one guest, since three hydroquinone molecules are sufficient to surround any one cage.

2. Tri-o-thymotide.—The dehydration of *o*-thymotic acid (2-hydroxy-6-methyl-3-isopropylbenzoic acid) with concentrated phosphoric acid gives a cyclic trimer that is capable of firmly retaining hexane, methanol, ethanol, xylene, benzene, chloroform, and many other compounds. X-ray diagrams have shown these complexes to be of the general clathrate type. However, one interesting fact arises: Since the size and location of the ring substituents prevent the molecule from assuming a planar configuration, it can exist in two stereoisomeric forms, depending on whether the element of symmetry is the axis of a left-handed or a right-handed spiral (III).

III

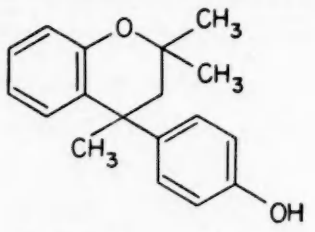


This property has been applied to resolve racemic mixtures (10). Tetrasalicylide, tetra-*m*- and -*p*-cresotide, and tetrathiosalicylide are included in this group.

3. Phenol.—Phenol will also give compounds of this general type. The host structure is again a trimer, as in hydroquinone, but the product has a rather loosely bound structure (11).

4. Condensation Product of Mesityl Oxide and Phenol.—In 1914, Dianin (12a) showed that the condensation product of mesityl oxide with phenol in the presence of HCl gave a monohydric phenol capable of forming crystalline addition compounds with acetic acid, chloroform, and ether. The significance of this property was not realized until 1955, when Baker and McOmie (12b) confirmed the formula suggested by Dianin and studied the behavior of this compound in the light of the recent developments on clathrate compounds. Measurements made on the crystalline mate-

IV



rial indicated a cagelike structure about twice as large as that of hydroquinone, and apparently formed from six molecules (IV). The ratio of host to guest can vary in this case from 6:1 down to 2:1, depending upon the size of the included molecule. Most of the organic solvents can be included by this compound.

Monomolecular Inclusion Compounds

Here the situation is encountered where there is just one host molecule for each guest, and, although they could be classified among the clathrates, since there is

a cagelike space in the center, the general characteristics of this group of compounds make it a type by itself.

A. Cyclodextrins.—These are crystalline cyclic glucosides first obtained by Schardinger in 1903 by the hydrolysis of starch with *Bacillus macerans* (13). The α-, β-, and γ-cyclodextrins appear to consist of six, seven, and eight glucose units, respectively, with corresponding internal diameters, 6 A., 8 A., and 10 A. Alternate names proposed for the cyclodextrins are: cycloamyloses (14) and glucanes (15).

These three compounds form a true homologous series, so that any prospective guest can be tried in each until one is found that will accommodate it. Numerous compounds can become included: benzene, naphthalene, bromobenzene, anthracene (3), octanol, trichloroethylene, *p*-nitrophenol, isopropylazulene, and others (1). The cyclodextrin inclusion compounds are very stable; some can even be recrystallized safely from water.

B. Bis-N,N'-alkylenebenzidines.—When benzidine reacts with an α,ω-dihalo paraffin, a molecule consisting of a large ring is obtained that is capable of crystallizing with one molecule of benzene or dioxane (16).

Macromolecular Inclusion Compounds

A somewhat different form of inclusion is found among several kinds of macromolecular compounds. This is accomplished, in some cases, through channels, but in many others rather in layers, the latter compounds having a stratified structure in which a guest can be accommodated between each stratum.

A. Zeolites.—These belong to the first type and show an appreciable resemblance to the urea and thiourea adducts, since the crystalline lattice is a veritable tridimensional net acting as a molecular sieve. The interstices are covered with water that can be eliminated by heat. The empty spaces thus formed can be filled with unusual amounts of gases, vapors, or dissolved compounds. A true solid solution is then formed in the interstices where only physical interactions take place. Chabazite and anazite (both activated) can enclose hydrocarbons with normal chains. This is true also of synthetic zeolites that can retain a very large number of compounds.

B. Bentonites (17).—These are of the second type. They are clays that have an extremely high swelling capacity, owing to the presence of montmorillonite. This mineral has a typical stratified structure that is capable of enclosing large quantities of compounds with polar groups, introducing slight modifications in the spaces between the layers.

Products of the Blue Iodine Reaction

Here the unusual situation is encountered where a single guest compound can be accommodated by a variety of host compounds.

No suitable explanation of the well-known reaction between starch and iodine was found until inclusion compounds were identified as such. The suggestion was first made by Freudenberg that the iodine was located in the central channel of the screwlike structure of the starch molecule. Substances other than starch are capable of including iodine to give blue addition compounds; for example, the flavones, coumarin, benzophenone, benzamide, and barbituric acid (18).

Applications

Separation of Compounds from Complex Mixtures.—This can be achieved successfully through urea, thiourea, and desoxycholic acid adducts and the zeolites. They are highly specific, as already indicated, and the procedures are simple enough to

make them of practical use. Applications to analytical procedures have also been successful (5).

Prevention of Oxidation.—In many cases, compounds that are sensitive to aerial oxidation can be protected by inclusion in the structure of a host. Such is the case of unsaturated fatty acids in urea (e.g., linoleic and linolenic acids and Vitamin A palmitate). The same protection can also be obtained with desoxycholic acid and cyclodextrin derivatives.

Separation of Optical Isomers.—Several compounds that are capable of acting as hosts have steric features such that their crystals are formed according to preferred directions. This makes them quite suitable for the resolution of racemic mixtures. This can be done with urea, thiourea, tri-*o*-thymotide and its related compounds (see Sect. B, d,*2*), and the cyclodextrins (1).

Preparation of Surface-Active Agents.—A new class of solid, nonionic, surface-active agents has been prepared by Barker and Ranauto (19) by making the urea adducts of simple polyethylene glycols or of any aliphatic or alkyl-aryl compound with a long, polyethylene glycol chain. The latter provides a molecule that has both a hydrophilic and a hydrophobic part. The preparation of the adducts is very simple, and they are reported to have the excellent soil-removal properties of nonionic detergents.

Drying Agents.—After being dried under heat, synthetic zeolites are capable of adsorbing a large amount of moisture, thus becoming very useful desiccants. Such zeolites are often referred to as "molecular sieves."

Equilibrium Displacements.—The formation of an inclusion compound with one of the products formed in an equilibrium reaction will cause the reaction to go to completion, e.g., in the acid-catalyzed conversion of 2-monoglycerides to 1-monoglycerides urea fulfills this condition since it will form an adduct only with the latter (20).

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